

Guidance for Industry

Submission of Documentation in Drug Applications for Container Closure Systems Used for the Packaging of Human Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability published in the *Federal Register*. For questions about this draft document, contact Alan Schroeder (301) 827-1050.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
June 1997**

Table of Contents

I.	INTRODUCTION	1
A.	Purpose	1
B.	Definitions	2
C.	CGMP and USP Requirements	3
D.	Information for IND vs. NDA/ANDA/AADA/BLA/PLA Submissions	4
1.	IND Applications	4
2.	NDA, ANDA, AADA, BLA, and PLA Submissions	5
E.	Packaging of a Drug Product by Another Firm	5
1.	Contract Packager	5
2.	Repackager	5
II.	QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS	6
A.	Introduction	6
B.	General Considerations	7
1.	Suitability for the Intended Use	7
2.	Quality Control of Packaging Components	13
3.	Secondary Packaging Components	15
C.	Information That Should Be Submitted in an Original Application for Any Drug Product	17
1.	Description	17
2.	Information About Suitability	17
3.	Information About Quality Control	19
4.	Stability Data (Packaging Concerns)	21
D.	Inhalation Drug Products	23
1.	Metered Dose Aerosols	23
2.	Inhalation Solutions	25
3.	Inhalation Powders (Dry Powder Inhalers)	25
4.	Nasal Sprays	26
E.	Drug Products for Injection and Ophthalmic Drug Products	29
1.	Injectable Drug Products	30
2.	Ophthalmic Drug Products	31
F.	Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems	34
1.	Liquid-Based Oral Drug Products	34
2.	Topical Drug Products	36
3.	Topical Delivery Systems	37
G.	Solid Oral Dosage Forms and Powders for Reconstitution	40
H.	Other Dosage Forms	44
III.	POST-APPROVAL PACKAGING CHANGES	44

A.	Changing from One Container Closure System to Another	44
B.	Changing the Size of a Container Closure System	45
C.	Changing to an Equivalent Container Closure System	45
1.	Changing Resins	45
2.	Changing Manufacturers of Packaging Components	46
D.	Packaging Equivalency Protocols	47
IV.	TYPE III DRUG MASTER FILES	48
A.	General Comments	48
B.	Typical Information Found in Type III DMFs	48
1.	Information About Suitability	48
2.	Information About Quality Control	49
V.	BULK CONTAINERS	49
A.	Containers for Bulk Drug Substances	49
B.	Containers for Bulk Drug Products	50
ATTACHMENT A	A-1
REGULATORY REQUIREMENTS	A-1
1.	The Federal Food, Drug, and Cosmetic Act	A-1
2.	The Code of Federal Regulations	A-2
3.	U.S. Pharmacopeia/National Formulary	A-4
ATTACHMENT B	B-1
COMPLIANCE POLICY GUIDES THAT CONCERN PACKAGING FOR		
HUMAN DRUGS (AND, WHERE APPLICABLE, BIOLOGICS)	B-1
ATTACHMENT C	C-1
EXTRACTION STUDIES	C-1
ATTACHMENT D	D-1
ABBREVIATIONS	D-1
Table One	7
Table Two	12
Table Three	22
Table Four	27
Table Five	32
Table Six	34
Table Seven	39
Table Eight	43

Draft - Not for implementation

GUIDANCE FOR INDUSTRY¹

SUBMISSION OF DOCUMENTATION IN DRUG APPLICATIONS FOR CONTAINER CLOSURE SYSTEMS USED FOR THE PACKAGING OF HUMAN DRUGS AND BIOLOGICS

I. INTRODUCTION

A. Purpose

This document is intended to provide guidance on general principles² for submitting information on packaging materials used for human drugs and biologics.³ This document supersedes the FDA's *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*, issued in February 1987.

The need for adequate information related to packaging materials for human drug products is imposed by the Federal Food, Drug, and Cosmetic Act (the Act), which states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health..." (§ 501(a)(3)). In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions; and section 505 of the Act requires a full

¹ This guidance has been prepared by the Packaging Technical Committee of the Chemistry, Manufacturing and Controls Coordinating Committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on container closure systems for the packaging of human drugs and biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For additional copies of this guidance contact the Drug Information Branch, Division of Communications Management, HFD-210, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857 (Tel.) 301-827-4573, (Internet) <http://www.fda.gov/cder/guidance.htm>.

² In general, this guidance does not suggest specific test methods and specifications (except for references to USP methods), nor does it suggest comprehensive lists of tests. These details should be determined based on good scientific principles for each specific container closure system for particular drug product formulations, dosage forms and routes of administration. Specifications should be based on actual data for particular packaging components and container closure systems, and they should be set to ensure batch-to-batch uniformity of packaging components.

³As used in this guidance, the terms "drug" and "drug product" include biological drugs unless otherwise noted.

Draft - Not for implementation

description of the methods used in, and the facilities and controls used for, the packaging of drugs. (See Attachment A.1.)

Approaches different from those described in this guidance may be followed, but the applicant is encouraged to discuss significant variations in advance with the appropriate FDA reviewers. This is to prevent applicants or sponsors from spending unnecessary time and effort in preparing a submission that the FDA may later determine to be unacceptable.

Section 505 of the Act states that an application shall include a description of the methods, facilities and controls used in packaging a drug product. This guidance, however, is not intended to describe the kinds of information that should be provided about packaging operations. This information may be addressed when the current CDER *Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products* is revised.

This guidance may be amended from time to time as the Agency recognizes the need through its regulatory efforts and through comments submitted by interested persons.

B. Definitions⁴

Materials of construction refer to the substances (e.g., glass, high density polyethylene (HDPE) resin, metal) used to manufacture a packaging component.

A *packaging component* means any single part of a container closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners, closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals (LVPs)), overwraps, administration accessories and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form.

A *container closure system* refers to the sum of packaging components that together contain and protect the dosage form. A *packaging system* is equivalent to a container closure system.

⁴ The definitions presented here are not intended to supersede the definitions of container and package in FDA's biologic regulations at 21 CFR 600.3.

Draft - Not for implementation

A *package* or *market package* refers to the container closure system and associated labeling and external packaging (e.g., cartons, shrink wrap, package insert) that constitute the article provided to a pharmacist or retail customer upon purchase. It does not include external packaging used solely for the purpose of shipping such articles.

Packaging materials may refer to packaging components or to materials of construction.

Quality refers to the physical and chemical attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use, and is also understood in this guidance to convey the associated properties of identity, strength and purity (e.g., 21 CFR 211.94(a)).

An *extraction profile* refers to the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A *quantitative extraction profile* is one in which the amount of each detected substance is determined.

C. CGMP and USP Requirements

Current good manufacturing practice (CGMP) requirements for the control of drug product containers and closures are set forth in 21 CFR Part 211. An outline of these and other applicable regulatory requirements is provided in Attachment A of this guidance. In addition, a listing of Compliance Policy Guides that deal with packaging issues is provided in Attachment B.

The United States Pharmacopeial Convention has established requirements for drug product containers that are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary (USP/NF)*. For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well-closed or light-resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the *USP*; materials of construction are defined in the "General Chapters" (see Attachment A).

Draft - Not for implementation

D. Information for IND vs. NDA/ANDA/AADA/BLA/PLA Submissions

1. IND Applications

a. Phases 1 and 2

For the initial stages of investigational studies, an investigational new drug application (IND) should briefly describe the container closure systems and labeling used for the drug substance and the dosage form, as well as any precautions necessary to protect and preserve the product from the time of manufacture until the time of clinical use.

In these early stages, the IND should also indicate that appropriate stability studies⁵ with the appropriate packaging systems have been initiated. Subsequently, these studies should be expanded to include other container closure systems that may be considered suitable for distributing the dosage form.

b. Phase 3

When clinical studies advance into Phase 3 (involving greater patient population exposure to the drug), additional attention should be focused on the packaging systems for the drug product and related stability information. The information furnished on the chemical, physical, and biological characteristics of, and the test methods used for, the packaging system and individual packaging components should be directed toward fulfilling requirements for the future submission of a new drug application (NDA), biologics license application (BLA), or product license application (PLA). To facilitate the proper review of such application, by the end of Phase 3 the IND should contain complete information pertaining to the proposed market package for the drug product, including compatibility and some stability data. For drug products with complex container closure systems (e.g., inhalation aerosols), it is advisable to finalize the market package by the beginning of Phase 3.

⁵ For information on conducting stability studies, see the FDA's *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics* (Feb. 1987).

Draft - Not for implementation

2. NDA, ANDA, AADA, BLA, and PLA Submissions

Section II of this guidance describes the type of information concerning packaging components that should be provided in NDAs, abbreviated new drug applications (ANDAs), abbreviated antibiotic applications (AADAs), BLAs, and PLAs.

E. Packaging of a Drug Product by Another Firm

1. Contract Packager

A contract packager is a firm retained by the applicant to package a drug product. The drug product remains the property of the applicant at all stages of shipping, storage and packaging, and the applicant remains responsible for the quality of the drug product.

The information that should be submitted in an NDA, ANDA, AADA, BLA, or PLA on the materials used by a contract packager is no different from what should be submitted if the applicant did its own packaging. If the information is provided in a Drug Master File (DMF) instead of in the application, a copy of the Letter of Authorization (LOA) for the contract packager's DMF should be provided in the application.

2. Repackager

Repackagers buy a drug product from a manufacturer and repackage it for sale under a label different from the manufacturer's. The responsibility for the quality and stability of the repackaged drug product is the repackager's.

All significant phases of the manufacturing and processing of a drug product (including packaging or repackaging) should be described as part of an application (NDA, ANDA, AADA, BLA, or PLA) prior to its being marketed.⁶ The only exception is the repackaging of solid oral drug products for which an approved application already exists. These types of repackaged drug products may be marketed without prior Agency approval. However, the packaging operation still is required to be in compliance with CGMPs, and there are limits to the expiration

⁶ *FDA Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulation," 446.100, Jan. 18, 1991 (CPG 7132c.06).

Draft - Not for implementation

period that may be used with the repackaged product unless the repackager conducts stability studies.⁷

II. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A. Introduction

A container closure system to be used in the packaging of a human drug is approved as part of the application (NDA, ANDA or AADA) for the drug product. A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application is expected to contain enough information to show that each proposed container closure system is suitable for the drug product in question.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about packaging systems for injectable dosage forms or drug products for inhalation is often more detailed than what should be provided about packaging systems for solid oral dosage forms. More information usually should be provided for liquid-based dosage forms than for powders or solids, since liquid-based dosage forms are more likely to interact with packaging components.

The general pattern of concern about packaging systems for different classes of drug products is illustrated in Table One. The purpose of Table One is to indicate relative levels of concern for different dosage forms and routes of administration. This applies only to this guidance for the qualification of container closure systems.

For the purpose of this guidance, container closure systems for the most common types of dosage forms will be discussed in terms of four general categories: products for inhalation; injectable and ophthalmic products; topical drug delivery systems and liquid-based oral and topical products; and solid oral dosage forms and topical powders (see Table One).

⁷ *FDA Compliance Policy Guides*, "Expiration Dating of Unit Dose Repackaged Drugs," 480.200, Feb. 1, 1984, rev. Mar. 1995 (CPG 7132b.11).

Draft - Not for implementation

B. General Considerations

1. Suitability for the Intended Use

Every proposed packaging system should be shown to be *suitable* for its intended use: it should adequately *protect* the dosage form; it should be *compatible* with the dosage form; and it should be composed of materials that are considered *safe* for use with the dosage form and route of administration. If the packaging has a performance feature in addition to "containing" the product, the container closure system should be shown to function properly.

Table One:
Examples of Packaging Concerns for Common Classes of Drug Products

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
<u>Highest:</u> Inhalation and Injection Drug Products	Inhalation aerosols and solutions; Injections and Injectable suspensions*	Sterile Powders and Powders for Injection; Inhalation Powders	
<u>High:</u> Ophthalmic or Transdermal Drug Products	Ophthalmic solutions and suspensions; Transdermal ointments and patches; nasal aerosols and sprays		
<u>Low:</u> Oral or Topical Drug Products	Topical solutions and suspensions*; topical and lingual aerosols; oral solutions and suspensions*	Topical Powders; Oral powders	Tablets and capsules;

*For the purposes of this table, the term "suspension" is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.

General issues concerning protection, compatibility and safety are discussed below. In this guidance, drug delivery will be discussed only in connection with specific dosage forms and routes of administration (see sections II.D, II.E, II.F and II.G).

a. Protection

Container closure systems should provide a dosage form with adequate protection from all factors that are liable to cause a decrease in the quality of that dosage form over its shelf life. Common causes of such degradation are: absorption of moisture vapor, loss of solvent, microbial

Draft - Not for implementation

contamination, exposure to light, and exposure to reactive gases (e.g., oxygen). Drug products also suffer an unacceptable loss in quality if they are contaminated by filth.

Not all drug products are susceptible to degradation by all of these factors (note the following examples). Sensitivity to light is not characteristic of all drug products. Not all tablets are subject to loss of quality due to absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection is typically provided by opaque or amber-colored containers or by opaque secondary packaging (cartons or overwraps). The USP test for Light Transmission (<661>) is the most widely-used standard. Situations exist in which solid and liquid-based oral drug products have been stored exposed to light, because the opaque secondary packaging component(s) have been removed, contrary to the labeling and USP recommendation. Firms, therefore, may want to consider using additional or alternate measures to provide light resistance to these kinds of drug products.

Loss of solvent may occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks may develop through rough handling or by closures backing off due to the buildup of pressure during storage. Leaks may also occur in tubes due to a failure of the crimp seal.

Moisture vapor may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of an LDPE bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection since glass is relatively impermeable, glass containers are more effective only if there is a good seal between the glass container and the closure.

The ultimate proof of the ability of a container closure system to protect a dosage form is established by stability studies. Qualification tests can be used as preliminary screening tools, though in some cases a dosage form may require more protection than is provided by containers that meet typical specifications for drug product containers.

Draft - Not for implementation

b. Compatibility

Packaging components that are compatible with a dosage form will not interact with it to such an extent to cause unacceptable changes to the quality of either the dosage form or the packaging component.

Possible interactions include, for example: loss of potency (due to absorption or adsorption of the active drug substance, or degradation of the active drug substance induced by a chemical entity leached from a packaging component); reduction in the concentration of an excipient (due to absorption, adsorption or leachable-induced degradation); precipitation; changes in drug product pH; discoloration of either the dosage form or a packaging component; or increase in brittleness of a packaging component.

While some interactions between packaging components and dosage forms will be detected during qualification studies of container closure systems, others may not show up except under long-term stability studies. Any change noted during a stability study that may be attributable to interaction between the dosage form and packaging components should be investigated and acted upon, regardless of whether the stability study is being conducted for an original or supplemental application, or as fulfillment of a commitment to conduct post-approval stability studies.

c. Safety

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when treated with the drug product. This consideration is especially important for those packaging components which may be in direct contact with the dosage form, but it holds for any component from which substances may migrate into the dosage form (e.g., ink or adhesive components).

Determining that packaging components are safe for their intended use is not a simple process. A comprehensive study involves two parts: extraction studies to determine what chemical species migrate into the dosage form (and at what concentrations), and a toxicological evaluation of those substances to determine the safe level of exposure via that route of administration. This technique is used by the Center for Food Safety and Applied Nutrition (CFSAN) to evaluate the safety of substances that may

Draft - Not for implementation

become indirect food additives (e.g., for additives or polymers that may be used in packaging foods).⁸

The question of safety may be evaluated by alternate methods. One such approach, often used with oral dosage forms, is reliance on the food additive regulations (21 CFR 170-199) promulgated by CFSAN; these regulations may specify certain limitations pertaining to the use of specific materials for packaging foods. This approach may not be acceptable for liquid oral dosage forms (see section II.F.1 of this guidance).

For certain drug products (e.g., injectables, topicals, and ophthalmics), some reliance has been made on the USP Biological Reactivity tests (USP <87> and <88> or, for Elastomeric Closures for Injections, USP <381>).

For products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence.

In the final analysis, however, a standardized approach to the issue of determining the safety of packaging components has not been established for drug products.

d. Performance

Performance of the container closure system refers to the ability of the package to function in the manner for which it was designed. Container closure systems are often called upon to do more than simply "contain" the dosage form. Two major considerations when evaluating performance are container closure system functionality and drug delivery.

i. Container Closure System Functionality

Containers may be designed to improve patient compliance (e.g., caps which contain counters), minimize waste (e.g., two chamber vials or IV bags), improve ease-of-use (e.g., prefilled syringes), or have other functions.

ii. Drug Delivery

⁸ FDA. CFSAN. 1995. "Recommendations for Chemistry Data for Indirect Food Additive Petitions," Version 1.2, Chemistry Review Branch, Office of Pre-Market Approval, June 1995.

Draft - Not for implementation

Drug delivery refers to the ability of the package to deliver the dosage form in the amount or rate described in the package insert. Some examples of packaging systems for which drug delivery aspects are relevant are prefilled syringes, transdermal patches, metered tubes, dropper and spray bottles, dry powder inhalers and metered dose inhalers.

Container functionality and/or drug delivery are compromised when the package fails to operate as designed. Failure can result from misuse, faulty design, manufacture, assembly or wear and tear during use. Tests and specifications as related to dosage form delivery and container functionality should be appropriate to the particular dosage form, route of administration, and design feature.

e. Summary

Table Two summarizes typical packaging suitability considerations for common classes of drug products. It is intended only as a general guide.

Draft - Not for implementation

**Table Two:
Typical Suitability Considerations for Common Classes of Drug Products**

(See Explanation Below Table)

Route of Administration/ Dosage Form	SUITABILITY ¹			
	Protection	Compatibility	Safety	Performance/ Drug Delivery
Inhalation Aerosols and Solutions	L, S, M, W, G	Case 1c	Case 1s	Case 1d
Inhalation Powders	L, W	Case 3c	Case 5s	Case 1d
Injections, Injectable Suspensions ²	L, S, M, G	Case 1c	Case 2s	Case 2d
Sterile Powders and Powders for Injection	L, M, W	Case 2c	Case 2s	Case 2d
Ophthalmic Solutions and Suspensions ²	L, S, M, G	Case 1c	Case 2s	Case 2d
Topical Drug Delivery Systems	L, S	Case 1c	Case 2s	Case 1d
Topical Solutions and Suspensions ² , and Topical and Lingual Aerosols	L, S, M	Case 1c	Case 2s	Case 2d
Topical Powders	L, M, W	Case 3c	Case 4s	Case 3d
Oral Solutions and Suspensions ²	L, S, M	Case 1c	Case 3s	Case 2d
Oral Powders	L, W	Case 2c	Case 3s	Case 3d
Tablets and Capsules	L, W	Case 3c	Case 4s	Case 3d

¹ If there is a special performance *function* built into the drug product (e.g., counter cap), it is of importance for any dosage form/route of administration to show that the container closure system performs that function properly.

² For definition of the term "suspension," see footnote to table 1.

Explanation of Codes in Table 2:

Protection: **L** (protects from light, *if appropriate*), **S** (protects from solvent loss/leakage), **M** (protects sterile products or those with microbial limits from microbial contamination), **W** (protects from water vapor, *if appropriate*), **G** (protects from reactive gases, *if appropriate*)

Compatibility: **Case 1c:** Liquid-based dosage form that conceivably could interact with its container in all the ways described in section II.B.1.b. **Case 2c:** Solid dosage form until reconstituted; greatest chance for interacting with its

Draft - Not for implementation

container occurs after it is reconstituted. **Case 3c:** Solid dosage form with low likelihood of interacting with its container.

Safety:

Case 1s: USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, batch to batch monitoring of extractables. **Case 2s:** USP Biological Reactivity Test data at a minimum, possibly extraction/toxicological evaluation. **Case 3s:** Packaging components satisfy food additive regulations when used with aqueous-based solvents; use with non-aqueous based solvent systems or aqueous based systems containing co-solvents may require additional qualification (see section II.E.1). **Case 4s:** Packaging components satisfy food additive regulations. **Case 5s:** Packaging components satisfy food additive regulations and the mouthpiece meets USP Biological Reactivity Test criteria.

Performance/Drug Delivery:

Case 1d: Frequently a consideration in the suitability of a packaging system. **Case 2d:** May be a consideration. **Case 3d:** Rarely a consideration.

2. Quality Control of Packaging Components

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to maintain consistency in the packaging components. This entails routine testing to establish that each batch meets appropriate acceptance or release specifications. Adequate controls will limit unintended post-approval variations in the procedures or materials used to make a packaging component to prevent adverse affects on the quality of a dosage form.

Principal consideration is given to consistency in physical characteristics and chemical composition.

a. Physical Characteristics

The physical characteristics of interest include dimensional specifications (e.g., size, shape, neck finish, wall thickness, design tolerances), other physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., opacity, metering valve delivery volume, or the ease of movement of

Draft - Not for implementation

syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect permeability, drug delivery performance, or the ability of a container closure system to produce a good seal. Variation in any physical parameter is important if it can affect the quality of a dosage form.

b. Chemical Composition

Changes in the chemical composition of materials of construction may affect the safety of packaging components. New substances⁹ may be extracted into the dosage form, or the amount of known extractables may increase. Changes in chemical composition may also affect the compatibility, functional characteristics or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability).

Composition changes may occur as intentional changes in a formulation or in processing aids (e.g., using a different mold release agent) or they may occur through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than a change in the supplier of a pure chemical compound, since polymeric and natural materials are often complex mixtures. Composition changes may also occur when there are changes made to the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), new equipment, or both.

Any intentional change in a formulation by a packaging component manufacturer should be reported to the pharmaceutical firms who purchase that component and to any appropriate DMFs. A change in formulation is considered a change in the specifications for the packaging component, and a firm should not use the new component to market their drug product until a supplemental application for its use has been approved (21 CFR 314.70(b)(2)(vii), 601.12)¹⁰. Similarly, manufacturers who supply raw materials or intermediate packaging components should inform customers and update DMFs concerning any intended changes to formulations or

⁹ I.e., substances not determined to be safe by the USP Biological Reactivity Tests or some other toxicological evaluation conducted on the original packaging component as part of the qualifying process.

¹⁰ There may be some exceptions in accordance with 21 CFR 314.70(d).

Draft - Not for implementation

manufacturing procedures. Changes which seem innocuous may have unintended consequences on the dosage forms marketed in the affected packaging systems.

Stability studies may be used to monitor the consistency of container closure systems in terms of compatibility with the dosage form and the degree of protection provided to the dosage form. However, there is no general policy concerning the monitoring of packaging systems and components with regard to safety. One exception involves inhalation drug products, for which batch-to-batch monitoring of extraction profiles for polymeric and elastomeric components is a routine request (see section II.D).

3. Secondary Packaging Components

Secondary packaging components are not intended to make contact with the dosage form.¹¹ Examples are cartons which are typically constructed of paper or plastic, and overwraps which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic and/or paper. For example, secondary packaging components may serve one or more of the additional functions listed below:

- a. Provide protection from excessive transmission of moisture or solvents into or out of the primary packaging system;
- b. Provide protection from excessive transmission of gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the primary packaging system;
- c. Provide light protection for the primary packaging system;
- d. Protect primary packaging systems that are flexible or that may need extra protection from rough handling; or
- e. Provide an additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the primary packaging system from microbial intrusion).

¹¹ Note that primary packaging components (the primary packaging system) are those parts of a container closure system that are or may be in direct contact with the dosage form.

Draft - Not for implementation

When information on container closure systems is submitted to an application, the emphasis should normally be on the primary packaging components. For secondary packaging components, a brief description will often suffice unless they are purported to provide some additional measure of protection to the drug product. In that case, more complete information should be provided, along with data showing that the secondary packaging actually provides the additional protection as described. (See sections II.A and II.B of this guidance, which are primarily directed towards primary packaging components but may be used to qualify secondary packaging components for additional functions.)

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the primary packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of ink or adhesive components or from volatile substances present in the secondary packaging components. (For example, a solution dosage form packaged in LDPE containers was found to be contaminated by a volatile constituent of the secondary packaging materials that enclosed it.) In such cases, even the secondary packaging components must be considered potential sources of contamination and the safety of their materials of construction should be taken into consideration.

C. Information That Should Be Submitted in an Original Application for Any Drug Product¹²

1. Description

A general description of the entire container closure system should be provided. In addition, the following information should be provided for each individual component of the packaging system:

- a. Identification by product name, product code (if available), the name and address of the manufacturer, and physical description (e.g., type of packaging component, size, shape, and color).
- b. Identification of the materials of construction. Plastics, elastomers, coatings, adhesives and other such materials should be identified by a specific product designation (code name and/or code number) and

¹² See Table Three for addition information..

Draft - Not for implementation

the source (name of the manufacturer). Alternate materials of construction should be indicated.

Since it is assumed that virgin polymers and resins will be used in the manufacturing of drug product packaging components, any processes that involve regrind¹³ materials should be explicitly identified. Such processes, if proposed, will be evaluated on a case-by-case basis and may or may not be found acceptable for a given drug product. Post-consumer recycled materials should not be used to manufacture packaging components for drugs.

- c. Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, and depyrogenation).

2. Information About Suitability

- a. To help establish safety and to assure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component. The status with regard to the food additive regulations should be indicated for each chemical component with a specific citation to the applicable FDA regulation. All of this information may be submitted via a DMF.
- b. Test results from all appropriate qualification and characterization tests should be provided.

Results from the USP Biological Reactivity Tests and/or extraction data should be provided, as appropriate, to help establish the safety of packaging components.

These may include USP tests such as the tests for light transmission or chemical resistance of glass containers, as well as tests that may be specific to certain types of dosage forms.

¹³ The term "regrind" as used here means a plastic material from a fabricator's own production that has been reground after having been processed by molding, extrusion, etc. This material has not left the control of the fabricator. Both the composition of the plastic and the resin supplier should remain the same for the regrind as for the batch of plastic material to which it is added.

Draft - Not for implementation

Results from characterization tests (such as the USP Physicochemical Tests-Plastics) should be provided to verify the identity of packaging components and to show that they possess key properties typical for that kind of material.

For non-USP tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related USP test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test and its validation.

Tests on assembled container closure systems should be conducted by the applicant (or a testing laboratory commissioned by the applicant) and the test results should be provided in the application. Such tests, for example, may include vacuum leak testing, moisture permeation, and weight loss or media fill, where appropriate.

Tests on individual packaging components may be conducted by the manufacturer of the component and may be reported via a DMF.

3. Information About Quality Control

Fabricators/manufacturers of packaging components and the drug product manufacturers who use them share the responsibility for assuring the quality of packaging components. These firms should have quality control programs in place so that consistent components are produced. Drug product manufacturers must have inspection programs for incoming packaging components/materials (21 CFR 211.22, 211.84 and 211.122). Drug product manufacturers may accept shipments of packaging components based on Certificates of Analysis (COAs) from the supplier and an identification test, provided the results of COAs are periodically validated (21 CFR 211.84(d)(3)).

a. Applicants

The tests and methods that will be performed on each batch of a packaging component received by the firm should be described. If batches usually will be accepted based on a supplier's COA, the tests and methods conducted for supplier validation should be described. (These should be the same specifications and tests indicated in the drug or biologic application for the component.)

Draft - Not for implementation

Dimensional and performance specifications should be provided. Specifications for extractables should be included, if appropriate.

Dimensional information is frequently provided via a detailed schematic drawing complete with dimensions and tolerances, and may be provided via the packaging manufacturer's DMF. A separate drawing may not be appropriate if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

When the consistency of the chemical composition of a packaging component is important, the appropriately validated test methods and specifications should be provided.

b. Manufacturers of Packaging Components Sold to Drug Product Manufacturers

Each manufacturer of a packaging component sold to a drug product manufacturer should provide descriptions of the quality control measures used to maintain consistency in the physical and chemical characteristics of the component. These generally include release specifications (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of packaging components is based on statistical process control,¹⁴ a complete description of the process (including control specifications) and its validation should be provided.

The description of the manufacturing process typically should be brief. It should include mention of any operations performed on packaging components after manufacture but prior to shipping (e.g., washing, coating, sterilization). In some cases it may be desirable for the description to be more detailed and to include in-process controls. This information may be provided via a DMF.

c. Manufacturers of Materials of Construction or of Packaging Components Used to Make Other Packaging Components

¹⁴ Statistical process control is defined as "[t]he application of statistical techniques for measuring and analyzing the variation in processes." Juran, J.M., ed., 1988, *Quality Control Handbook*, 4th ed., McGraw-Hill, p. 24.2.

Draft - Not for implementation

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or part on the quality control procedures of manufacturers who make intermediate packaging components that are combined to create the product. If so, each contributor to a final packaging component should provide descriptions of the quality control measures used to maintain consistency in the physical and chemical characteristics of the intermediate components.

Manufacturers of materials of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their products.

This information may be provided via a DMF.

4. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container closure systems proposed in the application for marketing. The packaging system used in each stability study should be clearly identified.

The container closure system should be monitored for signs of instability in drug product stability studies. When appropriate, an evaluation of the packaging system should be included in the protocol for stability studies. Even when a formal test for packaging quality is not included in a stability protocol, a firm should investigate any observed change in a packaging system used in stability studies. The observations, results of the investigation, and corrective actions should be reported. If the corrective action requires a change in an approved container closure system, a supplemental application may need to be submitted. Section III of this guidance describes the reporting requirements for post-approval changes to container closure systems.

For more complete information on conducting stability studies, the *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, and other current guidances on stability, should be consulted.

Draft - Not for implementation

**Table Three:
Information That Should Be Submitted in an Original Application for Any Drug Product**

Description	<p>Overall general description of the container closure system, plus: <u>For Each Packaging Component:</u> Name, product code, manufacturer, physical description Materials of construction (for each: name, manufacturer and product code) Description of any additional treatments</p>
Qualification (Suitability) and Characterization Tests	<p><u>Safety Data/Tests:</u> (on each component, as appropriate) Chemical composition of all plastics, elastomers, adhesives, etc.^a Citations to the food additive regulations Extraction studies Biological Reactivity Tests (USP <87> and <88>) Other tests as appropriate</p> <p><u>Protection Tests:</u> (on each component or the container closure system, as appropriate) Tests to measure protection from: Light Gases (e.g., oxygen) Moisture Solvent loss Microbial contamination (USP <61>, or test for sterility, USP <71>) Dirt/filth Other tests as appropriate</p> <p><u>Characterization Data/Tests:</u> (on each component) Tests on plastic components^b Tests on elastomeric components Tests on glass components</p> <p><u>Compatibility Tests:</u> (on each component or the packaging system, as appropriate) Container/dosage form interaction</p> <p><u>Performance Tests</u> (as appropriate; see section II.B.1.d)</p>
Quality Control	<p><u>For Each Packaging Component Received by the Applicant:</u> Applicant's acceptance tests and specifications^c Dimensional (drawing) and performance specifications Method to monitor consistency in composition, as appropriate</p> <p><u>For Each Packaging Component:</u> Manufacturer's release specifications, as appropriate Brief description of the manufacturing process</p>
Stability Data	See section II.C.4

Draft - Not for implementation

Footnotes to Table Three:

- a. Including any additives used in the manufacturing of a packaging component.
- b. Characterization tests for plastics should be performed on packaging components, not on the unformed resins.
- c. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, quality control and characterization sections of this table.

D. Inhalation Drug Products

Inhalation drug products include metered dose aerosols, inhalation solutions (administered via nebulizers), inhalation powders and nasal sprays. The chemistry, manufacturing, controls and preclinical considerations for inhalation drug products are unique from other dosage forms in that these drug products are intended for respiratory-tract compromised patients. This is reflected in the level of concern given to the nature of the packaging components which may come in contact with the dosage form or the patient (see Table One).

1. Metered Dose Aerosols

The container closure system for an oral inhalation aerosol (metered dose inhaler, or MDI) or a nasal aerosol (inhaler) is usually composed of a glass or metal canister, a metering valve (which may contain metal, elastomeric and plastic components), and a plastic actuator/mouthpiece (oral inhalation aerosols) or actuator (nasal aerosols). Elastomeric components seal the valve to the canister. Upon actuation of the valve, elastomeric components seal the valve's metering chamber from the rest of the canister to provide a single metered dose. The drug formulation may be a solution or the drug may be present in the form of a micronized suspension. A surfactant may be present to lubricate the valve and to prevent agglomeration of the drug suspension. The major constituent of the formulation is usually propellant(s).

The design, composition and tolerances of the closure components are unique in creating single metered doses of the drug formulation in the form of an aerosol spray with an appropriate spray pattern or plume geometry, particle size distribution, velocity leaving the actuator orifice, and content uniformity (based on the drug content of individual actuations). The dimensions and tolerances of the valve components and of the actuator (particularly the orifice in the actuator, which controls the spray) are all critical to the reproduction of the spray characteristics from container to container.

When fitted together, the canister and valve should be able to withstand the pressure of volatile propellants without leaking. The design characteristics of

Draft - Not for implementation

metered dose aerosols are normally sufficient to offer protection from some of the external factors that might otherwise cause degradation (e.g., light and oxygen). Moisture, however, may penetrate into the formulation if the drug product is stored under humid conditions.

A quantitative extraction profile should be obtained for each packaging component that may contribute leachables to the dosage form. That includes all plastic or elastomeric components of the valve and any residues (from manufacture or cleaning) and coating materials on the inside of the canister. A toxicological evaluation of these extractables should be made and results from the USP Biological Reactivity Tests (USP <87> and <88>) should be provided. As part of the packaging quality control program, the extraction profiles of all of these components should be monitored and controlled from batch to batch of each component. Once the reliability of the supplier has been established, based on multiple batches of each packaging component, reduced testing may apply.

Also, the profile of extractables in the drug product or placebo should be determined near the end of the product's shelf life and correlated, if possible, with the extraction profiles of the container and closure components. This profile of extractables in the drug product may be obtained with data collected beginning with the Phase 3 stability studies of the drug packaged in the to-be-marketed container closure system. Note that for ANDA applications, comparison of the extraction profiles of the container and closure components may be performed with the extractable profile of the drug product (or placebo) after storage under accelerated stability conditions for three months, along with a commitment to confirm the results for the drug product (placebo) on initial production stability batches at or near expiry.

Results from the USP Biological Reactivity Tests (USP <87> and <88>) should be also provided for the actuator. Extractables from the actuator should be periodically monitored and controlled as part of the acceptance testing of the actuator, to insure batch-to-batch reproducibility.

Acceptance tests and specifications for the valve and actuator should include dimensional measurements, extractable profile and performance characteristics (see Table Four).

For canisters, the description should include any treatment of the inside (e.g., surface treatment, coatings). Canister residues should be monitored and controlled.

Draft - Not for implementation

See Table Four for additional information.

2. Inhalation Solutions

Inhalation solutions are packaged in a variety of packaging systems, both single- and multiple-unit. Typically the containers are made of glass, LDPE or HDPE. The container closure system should protect the dosage form from loss of solvent, microbial contamination and, if appropriate, from exposure to light, gases and organic volatiles. Since the permeation of volatile contaminants through LDPE containers can be a problem, an overwrap (typically aluminum foil) may be used to decrease the overall permeability.

Results from USP Biological Reactivity Tests (USP <87> and <88>) and USP Physicochemical Tests-Plastics (USP <661>) should be provided for all packaging components that may contact the dosage form. For quality control, an extraction test using drug product or placebo should be performed on every batch of each plastic packaging component, with limits placed on the total weight of extractables. Once the reliability of the supplier has been established, based on multiple batches of each packaging component, reduced testing may apply. Depending on the level of non-volatile residue, specifications and tests may be needed to assure that a given extractable profile is maintained.

See Table Four for additional information.

3. Inhalation Powders (Dry Powder Inhalers)

All inhalation powders should be stored in container closure systems that provide protection from moisture. In some cases, protection from exposure to light should also be provided. Because the likelihood of migration of impurities from the container to the powder dosage form is expected to be low relative to other dosage forms, safety concerns will generally be satisfied if the primary packaging components all meet food additive regulations and the mouthpiece meets USP Biological Reactivity Test criteria (USP <87> and <88>). The appropriate review division in the Agency should be contacted concerning what safety data may be needed to support components that do not meet food additive regulations.

The flow resistance and design dimensions (e.g., air flow path, metering chamber, mechanical components) of the dry powder inhaler (DPI) device should be included in the device specifications. When appropriate, metering accuracy should be controlled. The extractable profile of the components of the DPI that contact either the patient's mouth or the drug should be monitored and controlled to insure

Draft - Not for implementation

batch-to-batch consistency in composition. Once the reliability of the supplier has been established, based on multiple batches of each packaging component, reduced testing may apply. Inconsistencies in the extraction profile should be investigated. A DPI should function appropriately and consistently over its expected lifetime under anticipated patient-use conditions.

See Table Four for additional information.

4. Nasal Sprays

Nasal sprays are aqueous drug formulations, either solutions or suspensions, which are packaged in multiple-unit bottles fitted with mechanical metering pumps and caps to protect the spray nozzle. Bottles may be made of HDPE or PET, for example, and the pumps are typically fabricated from various metal, plastic and elastomeric components. The plastic and elastomeric components are preferably manufactured from various materials approved by the FDA for food contact (for specified uses, see the indirect food additive regulations, 21 CFR 174-178)).

The container closure system should protect the dosage form from loss of solvent, microbial contamination and, if appropriate, from exposure to light and/or gases.

Results from USP Biological Reactivity Tests (USP <87> and <88>) and USP Physicochemical Tests - Plastics (USP <661>) should be provided for all plastic packaging components that may contact the dosage form. USP <381> test results should be provided for elastomeric components. For quality control, an extraction test (e.g., using water and any other components that may influence extractability) should be performed on every batch of each plastic and elastomeric packaging component, with limits placed on the total weight of extractables. Once the reliability of the supplier has been established, based on multiple batches of each packaging component, reduced testing may apply. Depending on the level of non-volatile residue, specifications and tests may be needed to assure that a given extractable profile is maintained.

See Table Four for additional information.

Draft - Not for implementation

**Table Four:
Information That Should Be Submitted for Inhalation Drug Products***

Description	Overall general description of container closure system, plus: <u>For Each Packaging Component:</u> a. Name, product code, manufacturer, physical description b. Materials of construction (for each: name, manufacturer and product code) c. Description of any additional treatments
Qualification (Suitability) and Characterization Tests	<u>Safety:</u> (Data for each component, as appropriate) <ul style="list-style-type: none">• Chemical composition of all plastics, elastomers, adhesives, etc.^a• Citations to the food additive regulations for all chemical components• For elastomeric or plastic components of MDI valves, and MDI container walls (coated or uncoated):<ul style="list-style-type: none">◦ a quantitative extraction profile, using the product vehicle as solvent (or a more effective extraction solvent), with identification of major components and toxicological evaluation of extractables◦ results from in vitro/in vivo biological testing (USP Biological Reactivity Tests <87> and <88>)• For MDI actuators and DPI mouthpieces: results from in vitro/in vivo biological testing (USP Biological Reactivity Tests <87> and <88>)

*See discussion in text for additional clarification.

Draft - Not for implementation

**Table Four:
Information That Should Be Submitted for Inhalation Drug Products**

Qualification (Suitability) and Characterization Tests (cont'd)	<p><u>Safety (cont'd):</u></p> <ul style="list-style-type: none"> For plastic packaging components for inhalation solutions and nasal sprays: <ul style="list-style-type: none"> an extraction study, using the drug product or placebo results from in vitro/in vivo biological testing (USP Biological Reactivity Tests <87> and <88>) For inhalation powders: the materials of construction for surfaces that will be in contact with the mouth or the dosage form should preferably meet food additive regulations (otherwise additional safety data may be required) <p><u>Protection:</u> (on each component or the container closure system, as appropriate)</p> <ul style="list-style-type: none"> Prevention of microbial contamination (evaluated on drug product) Protection against oxygen (e.g., MDIs; usually evaluated indirectly through stability testing) and organic volatiles (e.g., inhalation solutions) USP Light Transmission (when appropriate) Moisture vapor permeation (e.g., for inhalation powders and MDIs; evaluated on the drug product) Solvent Loss (e.g., for inhalation solutions and nasal sprays) Leak testing for MDIs (evaluated on the drug product) <p><u>Characterization:</u> (on each component)</p> <ul style="list-style-type: none"> USP Physicochemical Tests (USP <661> on all plastic components^b (inhalation solutions and nasal sprays) USP <381> test results for elastomeric components for nasal sprays Extractable profiles for elastomeric components for other inhalation drug products (e.g., MDIs) USP Chemical Resistance-Glass Containers tests for glass components (should meet Type I specifications) <p><u>Compatibility:</u> (on each component or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> For MDIs, metal containers and metal valve components should be evaluated for corrosion on storage (evaluated on drug product) <p><u>Drug Delivery Performance:</u> (on each component or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> For valves: performance tests and specifications (e.g., valve function, valve delivery, valve leakage) For actuators: performance tests and specifications (e.g., spray pattern, plume geometry and other tests for orifice defects) For DPIs: performance tests and specifications (e.g., resistance of the device and the air flow pathways; metering accuracy, where appropriate).
--	---

Draft - Not for implementation

**Table Four:
Information That Should Be Submitted for Inhalation Drug Products**

Quality Control	<p><u>For Each Packaging Component Received by the Applicant:</u></p> <ul style="list-style-type: none"> • Applicant's acceptance tests^c • Dimensional specifications and drawing • Performance specifications: <ul style="list-style-type: none"> ◦ E.g., for valves: valve function, valve delivery, valve leakage ◦ E.g., for actuators: spray pattern and other tests for orifice defects • Methods to monitor consistency in composition^d <ul style="list-style-type: none"> ◦ For elastomeric or plastic components of valves and container coatings (MDIs): an extraction profile on each batch with individual limits and test methods for all identified extractables (e.g., polynuclear aromatic hydrocarbons, nitrosamines, monomers, plasticizers, accelerators). Canister residues should be controlled. ◦ For actuators (MDIs) or plastic components of DPIs that contact drug or the patient's mouth: an extraction profile (must meet specifications) ◦ For plastic packaging components for inhalation solutions and nasal sprays: limits on extractables (individual and total), or (if the level of extractables is very low) limit on total weight of extractables (two or three individual extraction solvents should be employed). <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> • Manufacturer's release specifications, as appropriate • Description of the manufacturing process, as appropriate • Manufacturer's acceptance tests for each raw material used to fabricate packaging components and corresponding release specifications from the maker of the raw material
Stability Data	See Section II.C.4

- ^{a.} Including any additives used in the manufacturing of a packaging component.
- ^{b.} Characterization tests for plastics should be performed on packaging components, not on the unmolded resins.
- ^{c.} Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, quality control and characterization sections of this table.
- ^{d.} See text for comments about when it may be appropriate to reduce the frequency of extraction testing.

E. Drug Products for Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions or suspensions and are required to be sterile. Injectable dosage forms represent one of the highest risk drug products (see Table One), since any contaminants that are present (as a result of contact with the container or due to the container's failure to provide adequate protection) will be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally lower, any potential for causing harm to the eyes demands caution.

Draft - Not for implementation

1. Injectable Drug Products

Injectable drug products may be liquid-based in the form of solutions or suspensions, or solids in the form of sterile powders and powders for injection. The liquid-based products are classified as small-volume parenterals (SVPs) if they have a solution volume of 100 mL or less, or as large-volume parenterals (LVPs) if the solution volume exceeds 100 mL.¹⁵ Powders must be dissolved or dispersed in an appropriate solvent before being injected and sometimes come packaged with the solvent in the same container closure system.

An SVP may come packaged in a disposable cartridge, a disposable syringe, a vial, an ampule or a flexible bag. An LVP may come packaged in a vial, a flexible bag, a glass bottle or in some cases as a disposable syringe.

Cartridges, syringes, vials and ampules are usually composed of glass (types I or II) or polypropylene. Flexible bags are typically multilayered plastic. Stoppers and septa in cartridges, syringes and vials are elastomeric materials. The in-put (medication) and out-put (administration) ports for flexible bags may be plastic and/or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible primary container from rough handling.

The potential effects of container/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity; pyrogenic effects may result from the presence of impurities. The potency of the active drug substance or of antimicrobial preservatives may decrease due to absorption. Co-solvent systems essential to the solubilization of poorly soluble drugs can also serve as potent extractants of plastic additives. The complex mechanical construction of disposable syringes, which may be made of plastic, glass, rubber and metal components, provides a potential for interaction that is greater than that possible when a container consists of a single material.

Injectable drug products require protection from microbial contamination and may need to be protected from light or exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, while sterile powders or powders for injection may need to be protected from exposure to moisture vapor. All elastomeric materials used with injectable drug products should be tested

¹⁵ The terms SVP and LVP as used in this guidance correspond to the USP definitions of Small Volume Injection and Large Volume Injection, respectively (see the *U.S. Pharmacopeia/National Formulary*, Vol. 23/18, p. 1650 (1995)).

Draft - Not for implementation

according to USP <381>, Elastomeric Closures for Injectables. All plastics should meet the requirements of the USP Biological Reactivity Tests (USP <87> and/or <88>). Whenever possible, extracts for these tests should be obtained using the drug product vehicle. If the drug substance significantly affects extraction characteristics, the extracts should be obtained using the drug product. It may be advisable to obtain a quantitative extraction profile of elastomeric or plastic packaging components and to compare this periodically to new batches of the packaging components. Extractables should be identified whenever possible. Glass packaging components should meet the USP requirements. In some cases (e.g., when used to package some chelating agents), glass packaging components may need to meet additional specifications to prevent interactions between the components and the dosage form.

See Table Five for additional information.

2. Ophthalmic Drug Products

These drug products are usually solutions marketed, for example, in LDPE bottles with droppers built into the neck (sometimes referred to as "droptainers"), or ointments marketed in metal tubes with ophthalmic tips (see section II.F.2 for a more detailed discussion of tubes). A few solution products may still require glass containers due to stability concerns in packaging made of plastic. Ophthalmic ointments that are reactive toward metal may be packaged in tubes lined with an epoxy or vinyl plastic coating. Large volume intraocular solutions (for irrigation) may be packaged in glass or polyolefin (polyethylene and/or polypropylene) containers.

The American Academy of Ophthalmology (AAO) recommended to the FDA that a uniform color coding system be established for the caps and labels of all topical ocular medications. Applicants should follow this system or provide an adequate justification for any deviations to the system. The AAO color codes, as revised and approved by the AAO Board of Trustees in June 1996, are shown in Table Five.

Although ophthalmic drug products can be considered topical products (section II.F.2), they have been grouped here with injectables since they are required to be sterile (21 CFR 200.50(a)(2)). See Table Six for additional information.

Draft - Not for implementation

**Table Five:
Information That Should Be Submitted for Injectable or Ophthalmic Drug Products**

Description	<p>Overall general description of container closure system, plus:</p> <p><u>For Each Packaging Component:</u></p> <ol style="list-style-type: none"> Name, product code, manufacturer, physical description Materials of construction (for each: name, manufacturer and product code) Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components should be fully described) <p>Note: Silicone fluid (medical grade dimethicone) is often applied to needles of syringes and to elastomeric closures. The amount and source of the silicone should be reported. Since the presence of excess silicone fluid can interfere with tests for particulates, it is recommended that the amount of silicone fluid be minimized.</p>
Qualification (Suitability) and Characterization Tests	<p><u>Safety:</u> (Data for each component, as appropriate)</p> <ul style="list-style-type: none"> Chemical composition of all plastics, elastomers, adhesives, etc.^a For elastomeric closures: USP <381> Elastomeric Closures for Injections (includes USP <87> and <88> Biological Reactivity Tests) For plastic components and coatings for metal tubes: USP <87> and <88> Biological Reactivity Tests If the extracting properties of the drug product or the drug product vehicle may reasonably be expected to be different from that of water (e.g., due to high or low pH, or due to a solubilizing excipient), then extraction studies of elastomeric closures and other components should use the drug product or drug product vehicle; if the total weight of extracts significantly exceeds the amount obtained from water extraction, an extraction profile should be obtained For plastic components or elastomers that will be heat-sterilized, extraction profiles should be determined with extractions conducted at 121 °C for 1 hour instead of the usual USP extraction conditions <p><u>Protection:</u> (on each component or the container closure system, as appropriate)</p> <ul style="list-style-type: none"> USP <661> Light Transmission (when appropriate) Gases (e.g., oxygen) Moisture vapor permeation (powders) Solvent loss (liquid-based dosage forms) Sterility/container integrity <p>Other: Leak testing of tubes (ophthalmics)</p>

Draft - Not for implementation

**Table Five:
Information That Should Be Submitted for Injectable or Ophthalmic Drug Products**

Qualification (Suitability) and Characterization Tests (cont'd)	<p><u>Characterization:</u> (on each component)</p> <ul style="list-style-type: none"> • USP <661> Physicochemical tests on all plastic components^b • USP <381> Tests for Elastomeric Closures For Injectables • USP <661> Chemical Resistance-Glass Containers tests for glass components (usually Type I) <p><u>Compatibility:</u> (on each component or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> • For coatings for metal tubes: Coating integrity testing • For elastomeric components: Evaluation of swelling effects <p><u>Performance Tests:</u> (on each component or the packaging system, as appropriate) -- see section II.B.1.d</p>
Quality Control	<p><u>For Each Packaging Component Received by the Applicant:</u></p> <ul style="list-style-type: none"> • Applicant's acceptance tests^c • Dimensional (drawing) and performance specifications • Method to monitor consistency in composition (for most elastomeric components, some kind of revalidation (e.g., periodic evaluation of extraction profile) is recommended) <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> • Manufacturer's release specifications, as appropriate • Description of the manufacturing process, as appropriate, including procedures for sterilization and depyrogenation
Stability Data	See section II.C.4

- ^{a.} Including any additives used in the manufacturing of a packaging component.
- ^{b.} Characterization tests for plastics should be performed on packaging components, not on the unformed resins.
- ^{c.} Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, quality control and characterization sections of this table.

Draft - Not for implementation

**Table Six:
AAO Recommended Color Coding of Caps and Labels
for Topical Ophthalmic Medications**

Class	Color	Pantone Number
Anti-Infectives	Tan	467
Anti-Inflammatories/Steroids	Pink	197, 212
Mydriatics and Cycloplegics	Red	485C
Nonsteroidal Anti-Inflammatories	Gray	4C
Miotics	Green	374, 362, 348
Beta-Blockers	Yellow or Blue* Yellow C	290, 281
Adrenergic Agonists (e.g., Propine)	Purple	2583
Carbonic Anhydrase Inhibitors	Orange	1585
Prostaglandin Analogues	Turquoise	326C

*The AAO notes that as new classes of drugs are developed, this coding system may be modified in the future by reassigning the blue color to a new class of drugs while keeping yellow for beta-blockers.

F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products fall into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from packaging components into the dosage form. Although the higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms to be slower than for aqueous solutions, after extended contact the amount of leachables may depend more on their affinity for the liquid/semisolid phase than on the rate of migration.

1. Liquid-Based Oral Drug Products

Typical liquid-based oral dosage forms (as defined in USP <1151> Pharmaceutical Dosage Forms) are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters and suspensions. These products are usually non-sterile, but may be monitored for bio-burden or specific microbes.

These dosage forms are typically marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups which are intended to be used as is or admixed first

Draft - Not for implementation

with a compatible solvent or dispersant. Bottles are usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. Pouches may be single-layer plastic or laminated materials. Both bottles and pouches may use an overwrap, which is typically a laminated material. Cups may be metal or plastic with a heat-sealed lid made of a laminated material.

Liquid-based oral drug products typically need to be protected from solvent loss, microbial contamination and possibly from exposure to light.

There should be an absence of interactions between the container materials and the dosage form. Glass containers should meet USP requirements.

A patient's exposure to substances extracted from plastic packaging components into a liquid-based oral dosage form often will be comparable to a patient's exposure to the same substances through the use of similar materials to package food. In such cases, plastic packaging components will usually be considered safe for drug use if they meet FDA regulations for food additives. This assumption is usually considered valid for liquid-based oral dosage forms that patients will take only for a relatively short time (acute dosing regimen).

For liquid-based oral drug products that patients will continue to use for extended periods (e.g., months or years), packaging components that meet FDA requirements for food additives will be considered safe -- on that basis alone -- only if a patient's exposure to extractables can be expected to be no greater than the exposure through foods. For example, if the dosage form is aqueous-based and contains little or no co-solvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), compliance with food additive regulations will usually satisfy the issue of safety.

If the dosage form contains co-solvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), additional extractable information¹⁶ may be needed to address safety issues.

See Table Seven for additional information.

¹⁶ See Attachment C.

Draft - Not for implementation

2. Topical Drug Products

Topical dosage forms (as defined in USP <1151> Pharmaceutical Dosage Forms) include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions and suspensions. These dosage forms are generally intended for local (not systemic) effect and are often applied to skin or oral mucosal surfaces. The full range of topical products also includes some nasal and otic preparations as well as ophthalmic drug products. (As previously mentioned, because ophthalmic drug products must be sterile pursuant to 21 CFR 200.50, in this guidance they are discussed with injectables.) Vaginal and rectal drug products may be considered to be topical if they are intended to have a local effect.

Liquid-based topical products typically have a fluid or semi-solid consistency and are marketed in single- or multiple-unit containers (e.g., in rigid bottles or jars, collapsible tubes or flexible pouches). Powder products may be marketed in a sifter-top container. Antibacterial products may be marketed as sterile dressings. There are also a number of products marketed as pressurized aerosols or hand-pumped sprays.

Rigid bottles or jars are usually made of glass or polypropylene with a screw cap. The same cap liners and inner seals are sometimes used with solid oral dosage forms.

Collapsible tubes are usually metal or metal-lined, low-density polyethylene, or a laminated material. Tubes are fabricated by rolling and heat-sealing flat stock into a continuous tube of the desired diameter, then trimming to length and attaching the head by injection molding. The head insert is sometimes made of urea formaldehyde. Typically there is no cap liner. The inner seal may be plastic or metal which is heat-sealed into place or molded with the tube. The former may have a lip for removal by hand. The alternative is to incorporate a device into the construction of the cap for breaking the inner seal. The market package may include a separate applicator device or the applicator may be part of the closure.

Flexible pouches are usually single-unit or unit-dose packages. They may be fabricated from a single layer of plastic or from laminated materials which have been printed with the container label information.

Dressings consist of dosage form on a bandage material (typically Absorbent or Bandage Gauze) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Draft - Not for implementation

Unlike the aerosol products discussed in sections II.D.1 and II.D.4 (inhalation aerosols), topical aerosols are not intended to be inhaled. The droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin or mouth (lingual aerosol). Sprays for applying a suitable liquid dosage form may also be produced by hand pumps. Topical aerosols may be sterile or may contain a preservative to reduce the bioburden.

Packaging components for liquid-based topical products should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of packaging components should be evaluated according to the USP Biological Reactivity Tests (USP <87> and <88>).

See Table Seven for additional information.

3. Topical Delivery Systems

Topical delivery systems are self-contained, discrete dosage forms that are designed to deliver drug via intact skin or body surface. The USP defines three types of topical delivery systems: transdermal, ocular and intrauterine (USP <1151>).

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for seven days. Intrauterine systems are held in place without adhesive and may stay in place for a year.

A transdermal system is typically comprised of an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be composed of a plastic material impregnated with active ingredient(s) or a coated metal; it is shaped to remain in place after being inserted in the uterus.

Each of the systems is normally marketed in a single unit soft blister pack or a preformed tray covered with an overwrap.

See Table Seven for additional information.

Draft - Not for implementation

**Table Seven:
Information That Should Be Submitted for Liquid-Based Oral and
Topical Drug Products and for Topical Drug Delivery Systems**

Description	<p>Overall general description of container closure system, plus:</p> <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> a. Name, product code, manufacturer, physical description b. Materials of construction (for each: name, manufacturer and product code) c. Description of any additional treatments
Qualification (Suitability) and Characterization Tests	<p><u>Safety:</u> (Data for each component, as appropriate)</p> <ul style="list-style-type: none"> • Chemical composition of all plastics, elastomers, adhesives, etc.^a • For most liquid-based oral drug products: citations to the food additive regulations • For liquid-based oral drug products with chronic dosing regimens that contain alcohol or a co-solvent: information to show that the exposure to extractables will be no greater than that expected to result from the use of similar packaging components with foods,^b or that the exposure is acceptable based on toxicological data. • For packaging components for topical drug products, including coatings for metal tubes, and packaging components for drug delivery systems: USP Biological Reactivity Tests (USP <87> & <88>) <p><u>Characterization:</u> (on each component)</p> <ul style="list-style-type: none"> • USP <661> Physicochemical Tests on all plastic components^c • USP <661> Chemical Resistance-Glass Containers Tests for glass components <p><u>Protection:</u> (on each component or the container closure system, as appropriate)</p> <ul style="list-style-type: none"> • USP <661> Light Transmission (when appropriate) • Gases (e.g., oxygen) • Solvent Loss; plus USP <661> and <671> Moisture Vapor Permeation for liquid-based oral products (packaging systems should normally meet tight or class A specifications) • Microbial Contamination/container integrity (when appropriate) <p>Other: leak testing of tubes (topical drug products) and unit dose containers (liquid-based oral drug products)</p> <p><u>Compatibility:</u> (on each component or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> • For coatings for metal tubes: coating integrity testing <p><u>Performance Tests</u> (on each component or the packaging system, as appropriate) – see section II.B.1.d</p>

Draft - Not for implementation

**Table Seven:
Information That Should Be Submitted for Liquid-Based Oral and
Topical Drug Products and for Topical Drug Delivery Systems**

Quality Control	<p><u>For Each Packaging Component Received by the Applicant:</u></p> <ul style="list-style-type: none">• Applicant's acceptance tests^d• Dimensional (drawing) and performance specifications• Method to monitor consistency in composition, as appropriate <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none">• Manufacturer's release specifications, as appropriate• Description of the manufacturing process, as appropriate
Stability Data	See section II.C.4

- a. Including any additives used in the manufacturing of a packaging component.
- b. The materials of construction should be approved for contact with foods that have characteristics similar to those of the drug product (e.g., aqueous, acidic, alcoholic or fatty).
- c. Characterization tests for plastics should be performed on packaging components, not on the unformed resins.
- d. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, quality control and characterization sections of this table.

G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

It is generally recognized that the risk of interaction between packaging components and the dosage form is low with these kinds of dosage forms. Powders that are reconstituted in their market container, however, have an additional possibility for interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared to the container/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility of the container closure system is being evaluated.

Typical container closure systems are HDPE bottles with screw-on or snap-off closures and flexible packaging systems such as pouches or blister packages. For bottles, the container closure system is understood to mean a specific bottle and closure, and all of the components from which they are made. The closure is composed of a cap, often with a liner, and frequently with an inner seal. If used, fillers and desiccants are also considered primary packaging materials. A desiccant should differ in shape and/or size from the tablets or capsules with which it is packaged to prevent it from being mistaken for a unit of the dosage form.

The most frequent form of flexible packaging is blister packaging, which normally consists of a lidding material and a forming film. The lidding material is typically an aluminum

Draft - Not for implementation

laminate with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side. The sealing agent faces the product and the forming film. The forming film may be a single film, coated, or laminated. Pouches are laminates that are sealed at the edges by heat or adhesive.

Solid oral dosage forms generally need to be protected from potential adverse affects of moisture vapor. The presence of moisture may, for example, affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form.

To protect dosage forms in bottles from moisture vapor, the container should have both an intrinsically low rate of moisture vapor transmission and a good seal between the container and the closure. An applicant should specify the torque that will be applied to bottle closures during full-scale packaging operations and provide USP <671> test results showing that a good seal will be established at that torque. Specifications for moisture permeability should be based on test data for each specific container closure system, but should not be greater than 10 mg/day/liter.¹⁷ Similarly, leak test results should be provided for flexible packaging.

All container materials should meet indirect food additive requirements for contact with foods. Materials that have been approved only for contact with solid foods should not be used with powders for reconstitution if the powders are to be reconstituted in the market container.

The monographs for (purified) cotton and (purified) rayon in the USP provide acceptable standards for fillers for the packaging of tablets, with the following caveats: Cotton for use as a filler need not meet the USP monograph requirements for sterility, fiber length or absorbency; rayon for use as a filler need not meet the USP monograph requirements for fiber length or absorbency. Appropriate tests and specifications for identification and for moisture content should be developed for both cotton and rayon filler.

Rayon is a potential source of dissolution problems for gelatin capsules.¹⁸

See Table Eight for additional information.

¹⁷ See specification for water vapor permeation in the section for polyethylene containers in USP <661>.

¹⁸ Hartauer, K.J., et al., 1993, "The Effects of Rayon Coiler on the Dissolution Stability of Hard Shelled Gelatin Capsules," *Pharmaceutical Technology* 17: 76-83.

Draft - Not for implementation

**Table Eight:
Information That Should Be Submitted for Solid Oral Drug Products and Powders**

Description	<p>Overall general description of container closure system, plus:</p> <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> a. Name, product code & manufacturer b. Materials of construction c. Description of any additional treatments
Qualification (Suitability) and Characterization Tests	<p><u>Safety:</u> (Data for each component, as appropriate)</p> <ul style="list-style-type: none"> • Chemical composition of all plastics, elastomers, adhesives, etc.^a • Citations to the food additive regulations <p><u>Characterization:</u> (on each component)</p> <ul style="list-style-type: none"> • USP <661> Physicochemical Tests on all plastic components^b <p><u>Protection:</u> (on each component or the container closure system, as appropriate)</p> <ul style="list-style-type: none"> • USP <661> Light Transmission (when appropriate) • USP <661> and <671> tests for moisture vapor permeation <p>Other tests:</p> <ul style="list-style-type: none"> • Leak tests for unit-dose packaging <p><u>Compatibility:</u> (on each component or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> • As appropriate <p><u>Performance Tests</u> (on each component or the packaging system, as appropriate) – see section II.B.1.d</p>
Quality Control	<p><u>For Each Packaging Component Received by the Applicant:</u></p> <ul style="list-style-type: none"> • Applicant's acceptance tests^c • Dimensional (drawing) and performance specifications • Method to monitor consistency in composition, as appropriate <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> • Manufacturer's release specifications, as appropriate • Description of manufacturing process, as appropriate
Stability Data	See section II.C.4

^a. Including any additives used in the manufacturing of a packaging component.

^b. Characterization tests for plastics should be performed on packaging components, not on the unformed resins.

^c. Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, quality control and characterization sections of this table.

Draft - Not for implementation

H. Other Dosage Forms

When submitting information for dosage forms not specifically covered by the sections above, firms should take into consideration the compatibility and safety concerns raised by the route of administration of the drug product and the nature of the dosage form (solid or liquid-based), the kinds of protection the container closure system should provide to the dosage form, and the potential effect of any treatments or handling that may be unique to the drug product on the packaging system. Quality control procedures for all packaging components should be adequate to assure the maintenance of the safety and quality of future production batches of the drug product.

III. POST-APPROVAL PACKAGING CHANGES

A change in the container closure system approved in an application, a change to a different container closure system, or the addition of a new container closure system must be reported to the application. While some changes may be documented in annual reports (21 CFR 314.70(d)(6)), packaging changes described under 21 CFR 314.70(b)(2) must be reported via supplemental applications, and the supplements must be approved before the changes are placed into effect.

A. Changing from One Container Closure System to Another

A change from one container closure system to another or for the addition of a new container closure system falls under 21 CFR 314.70(b)(2)(vii) (or 21 CFR 601.12(b) for a biologic) and must be reported via a prior-approval supplemental application. The kind of information that should be submitted to support the new container closure system is the same as what should be submitted in an original application (see section II of this guidance).

Changes in the materials of construction of packaging components are also covered under 21 CFR 314.70(b)(2)(vii) and must be reported in prior-approval supplemental applications. Although the regulation cites the specific examples of changing from glass to plastic or from one type of plastic to another, any change in the materials of construction should be reported in a prior-approval supplement unless the change is to an equivalent material and the equivalency is documented according to an approved protocol¹⁹ (21 CFR 314.70(d)(6)).

B. Changing the Size of a Container Closure System

¹⁹ This refers to a protocol approved in the application or published in an official compendium (see section III.D).

Draft - Not for implementation

A change in only the size of a container (except for solid dosage forms) falls under 21 CFR 314.70(b)(2)(viii) (or 21 CFR 601.12(b) for a biologic) and must be reported via a prior-approval supplemental application. Any change in the dimensions of a packaging component is considered to constitute a change in its size.

Changes in container size for solid oral dosage forms may be documented in annual reports as indicated in 21 CFR 314.70(d)(8). This regulation is interpreted to apply only to changes to intermediate sizes that are bracketed by satisfactory stability data in the application. When the size of a new container and closure system is outside the range of sizes approved in the application, a prior-approval supplement should be filed for the change.

C. Changing to an Equivalent Container Closure System

Examples of changes to equivalent container closure systems include changing from one plastic resin to another of the same type or changing from one supplier of a packaging component to another. How these changes should be submitted depends on whether an equivalency protocol²⁰ has been established for the kind of change being proposed. The information submitted should describe the change completely and be sufficient to establish that the new packaging components are equivalent to those already approved. In some cases, especially if no equivalency protocol exists, as much information may have to be submitted as for an original application.

The following examples illustrate when changes to equivalent container closure systems should be documented in annual reports and when they should be reported via prior-approval supplements. The discussion is general and does not cover all contingencies.

1. Changing Resins

A change from one type of resin to another always falls under 21 CFR 314.70(b)(2)(vii) and must be reported in a prior-approval supplement.

A change from one resin to another resin of the same type (e.g., two HDPE resins) may be documented in an annual report provided there is a pre-existing equivalency protocol applicable to the situation. For example, if a new HDPE resin were to be used in containers for solid oral dosage forms in place of an already approved HDPE resin, the change could be documented in an annual report since an interchangeability protocol for equivalent HDPE resins exists in the

²⁰This refers to a protocol approved in the application or published in an official compendium. See section III.D.

Draft - Not for implementation

USP ("Polyethylene Containers," part of USP <661>). However, if the new HDPE resin were to be used in containers for liquid oral dosage forms, the change should be made via a prior-approval supplemental application unless an equivalency protocol were already approved in the application.

2. Changing Manufacturers of Packaging Components

Packaging components from different suppliers may be considered equivalent if they are made to the same specifications, from the same materials of construction, and according to the same method of manufacture. Equivalency still should be demonstrated by appropriate tests (e.g., in conformance with an approved equivalency protocol²¹), which may include stability information, as appropriate. If trade secrets are involved in the manufacturing of a packaging component, or if the method of manufacture is considered hard to replicate, similar packaging components from two different suppliers may not be considered equivalent unless they both pass the full range of qualification tests described in section II of this guidance. Because these conditions are frequently operative, most changes in supplier should be submitted in prior-approval supplemental applications.

Exceptions to this general rule include polyethylene containers for solid oral dosage forms and PET/PETG containers for liquid oral dosage forms. Interchangeability protocols exist for both of these changes in the USP. Glass containers from different suppliers also may be used interchangeably as long as they meet the specifications for the approved Type of glass (USP <661> Chemical Resistance--Glass Containers) and the dosage form in question is not unusually reactive toward glass. Changes of supplier for these types of packaging components may be documented in annual reports.²²

Changes in suppliers of materials used as filler in the packaging of solid oral dosage forms may be documented in an annual report provided the materials from each supplier meet the applicant's specifications. However, because switching from one type of filler to another has been found on occasion to affect the stability of drug products, a change of that nature should be reported via a prior-approval supplemental application.

D. Packaging Equivalency Protocols

²¹ This refers to a protocol approved in the application or published in an official compendium (see section III.D).

²² The documentation may include stability information, as appropriate.

Draft - Not for implementation

Packaging equivalency protocols are mentioned in 21 CFR 314.70(d)(6), which states that a change within the container and closure system may be documented in an annual report provided that the equivalency of the two systems can be demonstrated according to a protocol approved in the application or published in an official compendium.

The use of compendial equivalency protocols to relieve a firm from having to report certain changes via prior-approval supplements has been discussed above. Protocols in approved applications may be used the same way, but must be made part of an application first pursuant to 21 CFR 314.70(d)(6). Although the regulations do not specifically provide for the addition of a packaging equivalency protocol after an application has been approved, such a protocol may be considered a change in specifications for the container and closure system (21 CFR 314.70(b)(2)(vii)) and should be submitted in a prior-approval supplemental application.

Supplements for equivalency protocols should only involve changes to equivalent container closure systems. Protocols should not be proposed, for example, for changing from bottles to unit dose packaging, or from glass containers to HDPE, or from HDPE to PVC. Laminated materials may not be considered equivalent if two materials being compared have a different number of layers or if the types of materials of construction are different.

Proposed equivalence protocols should be backed by enough data to show that they are truly capable of establishing the equivalency of packaging components. At a minimum, protocols should show that new packaging components are equivalent to the approved components with regard to safety and compatibility, ability to protect the dosage form, and delivery performance characteristics (if the packaging is used to deliver the dosage form). A protocol should also take into consideration that some properties of a container closure system depend on the complete packaging system (e.g., moisture permeation depends in part on the seal between the container and the closure). The new container closure system should be added to the stability protocol. Although a commitment to perform additional stability studies may be acceptable, in some cases it may be more appropriate for stability data to be acquired before the change in packaging is implemented.

Draft - Not for implementation

IV. TYPE III DRUG MASTER FILES

A. General Comments

The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA, AADA, BLA, or PLA or the sponsor of an IND. Packaging information supplied to the applicant by the manufacturer of a packaging component (or material of construction) can be included directly in the application. Information that a manufacturer will not share with an applicant because it is considered proprietary may be placed in a DMF and incorporated in an application by reference.

Information in Type III DMFs is not restricted to that of a proprietary nature. DMF holders may include in DMFs as much or as little information on their packaging components as they choose. Manufacturers of packaging components are not required to have Type III DMFs on file. Without a DMF, however, there is no way for the FDA to review proprietary information without its being shared with the applicant.

The Agency ordinarily reviews DMFs only in connection with an IND, NDA, ANDA, AADA, BLA, or PLA. If the combined information from the application and the DMF is not satisfactory, the Agency may request additional information from either the applicant or the DMF holder.

General information on the physical formatting of DMFs and Letters of Authorization may be found in the CDER *Guideline for Drug Master Files*.

B. Typical Information Found in Type III DMFs

Section II of this guidance discusses the kind of information the Agency usually reviews concerning packaging components for drug products. The following are the items that are most likely to be submitted via DMF:

1. Information About Suitability:
 - a. The complete chemical composition should be provided for every material used in the manufacture of a packaging component. The status with regard to the food additive regulations should be indicated for each chemical component, with a specific citation to the applicable FDA regulation.
 - b. Appropriate qualification and characterization tests should be conducted on individual packaging components.

Draft - Not for implementation

2. Information About Quality Control:

- a. Dimensional (drawing) and performance specifications.
- b. Descriptions of the quality control measures used to maintain consistency in the physical and chemical characteristics of packaging components:

A description of the specifications used for batch release testing of packaging components should be provided. If release of the packaging components is based on statistical process control, then a summary of the QA/QC specifications for this process should be provided.

A description of the manufacturing process for the packaging component and of any operations performed on packaging components after manufacture but prior to shipping (e.g., washing, coating, sterilizing) should be provided.

V. BULK CONTAINERS

A. Containers for Bulk Drug Substances

Drug substances are typically solids, but some are liquids or gases.

Containers for the storage or shipment of bulk solid drug substances are typically drums with LDPE liners. The liners, two of which are generally used, are usually heat-sealed or closed with a twist tie. Desiccants may be placed between the bags.

The drum provides protection from light and mechanical strength to protect the liner during shipment and handling. The majority of the protection from contamination by air and moisture is provided by the liner. Since LDPE is not a particularly good barrier against moisture vapor permeation, drug substances that are sensitive to moisture may need additional protection. Alternatives to LDPE bags, such as heat-sealable laminates with comparatively low rates of moisture vapor transmission, may be more appropriate for sensitive drug substances.

Qualification of the container is typically based on the compatibility and safety of the liner, but may include characterization of the container for solvent or gas transmission (see section II.B of this guidance).

Draft - Not for implementation

Containers for the storage or shipment of bulk liquid drug substances are typically made of plastic, stainless steel, or glass- or epoxy-lined metal, and have rugged, tamper-resistant closures. Qualification of the container should include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components (see section II.B of this guidance).

A drug application (or Type II DMF) should include a detailed description of the container used for packaging bulk drug substance, including the specific container, closure, all liners, liner closure and desiccant (if any), and the composition of each. The regulatory status of the primary packaging components under the food additive regulations should be cited. Release/acceptance tests for the packaging components should be indicated.

Stability studies to establish a retest period for a bulk drug substance should be conducted with fillers or desiccant packs in place (if used). Smaller versions of the actual container may be used. Stability recommendations for containers of different types are described in the Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.

Containers for gases are covered by Department of Transportation regulations.

B. Containers for Bulk Drug Products

Containers for bulk drug products may be used for storage prior to packaging or for shipment to repackagers or contract packagers. In all cases, the containers should be of such design as to adequately protect the dosage form and should be constructed of materials that are compatible and safe.

On-site storage containers have generally been considered a CGMP issue under 21 CFR 211.65. However, if a firm plans to hold a drug product in bulk storage for a long time (e.g., more than three months), the storage containers and the storage time should be described in the drug application. In addition, due consideration should be given to the collection of stability data to demonstrate that extended storage in the described containers does not adversely affect the dosage form. Even when the storage time before packaging will be short, firms should use bulk storage containers that provide adequate protection and that are manufactured of compatible and safe materials (see section II.B of this guidance).

Containers for the transportation of bulk dosage form to contract packagers (section I.E.1) should be described in drug applications. These containers should be adequate to protect the dosage form and should be constructed of compatible and safe materials. The

Draft - Not for implementation

protective properties of such shipping containers are verified by the practice of subjecting annual batches of the packaged product to stability studies. Some information should be provided to show that the container materials are safe (see section II.B of this guidance).

Containers specifically intended for the transportation of large volumes of dosage form to a repackager (section 1.E.2), whether for solid or liquid dosage forms, are considered market packages. They should meet the same requirements for protection, compatibility and safety as smaller market packages,²³ and should be fully described in an application. The length of time the dosage form will spend in the bulk containers may be a factor in determining the level of detail of the supporting information. Examples of large-volume shipping packages include a 10,000-tablet HDPE pail with tamper evident closure or a 10-liter PET container with a screw cap closure with dispenser attachment for a liquid drug product to be sold to mass distribution pharmacies. A special case is the Pharmacy Bulk Package described in USP 23 <1>.

²³ *FDA Compliance Policy Guides*, "Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulation," Section 446.100, Jan. 18, 1991 (CPG 7132c.06).

REGULATORY REQUIREMENTS

1. The Federal Food, Drug, and Cosmetic Act

a. Section 501

A drug shall be deemed to be adulterated “if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health” (§ 501(a)(3))

b. Section 502

A drug or device shall be deemed to be misbranded

“[i]f it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein” (§ 502(g))

“[i]f it is a drug and its container is so made, formed, or filled as to be misleading” (§ 502(i)(1))

“[i]f it is a drug and its packaging or labeling is in violation of an applicable regulation issued pursuant to section 3 or 4 of the Poison Prevention Packaging Act of 1970” (§ 502(p))

c. Section 505

“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug” (§ 505(a)).

Section 505(b)(1)(D) requires "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug."

Draft - Not for implementation

2. The Code of Federal Regulations

a. 21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals

i. Subpart E, Control of Components and Drug Product Containers and Closures (21 CFR 211.80 - 211.94)

In particular, 21 CFR 211.94 outlines the requirements for drug product containers and closures:

- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
- (c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.
- (d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

ii. Subpart F, Production and Process Controls (21 CFR 211.100 - 211.115)

iii. Subpart G, Packaging and Labeling Control (21 CFR 211.122 - 211.137)

In particular, 21 CFR 211.132 describes the tamper-resistant packaging requirements for over-the-counter (OTC) human drug products. Most OTC drug products must be packaged in tamper-resistant containers.

Draft - Not for implementation

iv. Special Packaging

As defined in section 2(4) of the Poison Prevention Packaging Act of 1970 and as implemented in 16 CFR Part 1700, special packaging “means packaging that is designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time and not difficult for normal adults to use properly, but does not mean packaging which all such children cannot open or obtain a toxic or harmful amount within a reasonable time” (21 CFR 310.3(l)).

The regulations in 16 CFR Part 1700 were updated on July 21, 1996. The revised regulations require testing of a drug package by senior adults (ages 50-70) to demonstrate that the package is not difficult for them to use properly.

This requirement causes no difficulty in the case of an NDA or an ANDA submission since the application should contain a full description of the container closure system, as well as pertinent suitability studies.

The requirement applies not only to the familiar screw cap but also to blister packaging. In the latter case, child-resistant packaging is usually achieved by modifying materials of construction or dimensions so that the package is resistant to tear or rupture in the hands of a child.

b. 21 CFR 170-199 - Food Additive Regulations

Those that are applicable to packaging components are:

- i. Part 174 - Indirect Food Additives: General
- ii. Part 175 - Indirect Food Additives: Adhesives and Components of Coatings
 - e.g., 175.105 Adhesives
 - 175.300 Resinous and polymeric coatings
- iii. Part 176 - Indirect Food Additives: Paper and Paperboard Components
 - e.g., 176.170 Components of paper and paperboard in contact with aqueous and fatty foods

Draft - Not for implementation

176.180 Components of paper and paperboard in contact with dry food

iv. Part 177 - Indirect Food Additives: Polymers

e.g., 177.1380 Fluorocarbon resins
 177.1520 Olefin polymers
 177.1630 Polyethylene phthalate polymers

v. Part 178 - Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers

vi. Part 186 - Indirect Food Substances Affirmed as Generally Recognized as Safe (GRAS)

e.g., 186.1673 Pulp

c. Other Sections

i. 21 CFR 201 - Labeling

ii. 21 CFR 310.509 - Parenteral drug products in plastic containers

iii. 21 CFR 200.50(a)(3) - Containers of ophthalmic preparations

3. U.S. Pharmacopeia/National Formulary

The following sections are applicable to packaging components:

a. General Notices - PRESERVATION, PACKAGING, STORAGE, AND LABELING

b. General Tests and Assays

<1> Injections
<87> Biological Reactivity Tests, In Vitro
<88> Biological Reactivity Tests, In Vivo
<161> Transfusion and Infusion Assemblies

Draft - Not for implementation

- <381> Elastomeric Closures for Injections
 - Biological Test Procedures
 - Physicochemical Test Procedures
- <601> Aerosols
- <661> Containers
 - Light Transmission
 - Chemical Resistance - Glass Containers
 - Biological Tests - Plastics and Other
 - Polymer
 - Physicochemical Tests - Plastics
 - Containers for Ophthalmics - Plastics
 - Polyethylene Containers
 - Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles
 - Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms
 - Customized Patient Medication Packages
- <671> Containers - Permeation
 - Multiple-Unit Containers for Capsules and Tablets
 - Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets
- <691> Cotton (or the monograph for Purified Rayon USP)
- <771> Ophthalmic Ointments
- <1151> Pharmaceutical Dosage Forms

Draft - Not for implementation

ATTACHMENT B

**COMPLIANCE POLICY GUIDES THAT CONCERN PACKAGING FOR
HUMAN DRUGS (AND, WHERE APPLICABLE, BIOLOGICS)
(August 1996)**

Compliance Policy Guides are issued by the Division of Compliance Policy (in the Office of Enforcement/Office of Regulatory Affairs), which is not part of CDER or CBER. The following listing of Compliance Policy Guides that concern packaging is provided for information only. Any questions or concerns about the content of any Compliance Policy Guide should be addressed to the Division of Compliance Policy.

Sub Chapter 410	Bulk Drugs
Sec. 410.100	Finished Dosage Form Drug Products in Bulk Containers - Applications of Current Good Manufacturing Practice Regulations (CPG 7132a.06)
Sub Chapter 430	Labeling and Repackaging
Sec. 430.100	Unit Dose Labeling for Solid and Liquid Oral Dosage Forms (CPG 7132b.10)
Sec. 430.200	Repacking of Drug Products - Testing/Examination Under CGMPs (CPG 7132.13)
Sub Chapter 440-448	New Drugs
Sec. 446.100	Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or Other Manipulations (CPG 7132c.06)
Sub Chapter 450-457	OTC
Sec. 450.500	Tamper-Resistant Packaging Requirements for Certain Over-the-Counter (OTC) Human Drug Products (CPG 7132a.17)

Draft - Not for implementation

Sec. 450.550	Control and Accountability of Labeling Associated with Tamper-Resistant Packaging of Over-the-Counter Drug Products (CPG 7132.14)
Sub Chapter 480	Stability/Expiration
Sec. 480.100	Requirements for Expiration Dating and Stability Testing (CPG 7132a.04)
Sec. 480.200	Expiration Dating of Unit Dose Repackaged Drugs (CPG 7132b.11)
Sec. 480.300	Lack of Expiration Date of Stability Data (CPG 7132a.10)

EXTRACTION STUDIES

An extraction study of a packaging component typically involves exposing a sample of the component, often subdivided into small pieces to increase surface area, to an appropriate solvent system at elevated temperatures, followed by chemical analysis. The purpose of using elevated temperature is to increase the rate of extraction, so that a short experimental time may simulate a longer exposure time at room temperature, or to maximize the amount of extractables obtained from a sample.

The methods employed to analyze the resulting extracts vary depending on the purpose of the extraction study and the nature of the packaging component. The extraction solvent may be evaporated to concentrate the extracts or to determine the total weight of non-volatile extractables. HPLC or gas chromatography may be used to obtain qualitative or quantitative extraction profiles of volatile or non-volatile extractables.

Extraction studies may be conducted during the qualification of packaging components for any of the following purposes:

- To perform USP characterization tests on plastics (USP <661>) or elastomers (USP <381>),
- To perform USP Biological Reactivity Tests (USP <87> and <88>) on plastics or elastomers,
- To obtain qualitative extraction profiles of plastics or elastomers,
- To obtain quantitative extraction profiles of plastics or elastomers, or
- To evaluate whether FDA food additive regulations provide an adequate indicator of safety.

Extraction studies may also be conducted on a routine basis as a quality control measure to monitor the chemical compositions of elastomeric or other packaging components.

Draft - Not for implementation

The solvent that should be used in an extraction study depends on the purpose of the study. The ideal situation is for the extracting solvent to have the same propensity to extract substances as the dosage form. The preferred solvent is normally the drug product or placebo vehicle. When feasible, the dosage form itself should be used.

ABBREVIATIONS

AADA	Abbreviated Antibiotic Application
AAO	American Academy of Ophthalmology
ANDA	Abbreviated New Drug Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CGMP	Current Good Manufacturing Practice
COA	Certificate of Analysis
CVM	Center for Veterinary Medicine
DMF	Drug Master File
DPI	Dry Powder Inhaler
FDA	U.S. Food and Drug Administration (the Agency)
HDPE	High Density Polyethylene
IND	Investigational New Drug Application
LDPE	Low Density Polyethylene
LOA	Letter of Authorization
LVP	Large-Volume Parenteral
MDI	Metered Dose Inhaler
NDA	New Drug Application
PET	Polyethylene Terephthalate
PETG	Polyethylene Terephthalate G
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
SVP	Small-Volume Parenteral
USP/NF	U.S. Pharmacopeia/National Formulary